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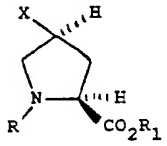
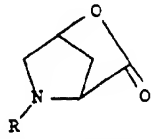
(58) Field of search
C2C

(54) Process for preparing (trans)–4–phenyl–L–proline derivatives

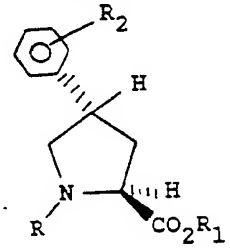
(57) (Trans)–4–phenyl–L–proline derivatives, which are useful in preparing certain angiotensin converting enzyme inhibitors, are prepared by reacting a compound of formula



or



wherein R is a nitrogen protecting group, R_1 is H, aryl, arylalkyl or lower alkyl, and X is a leaving group with an aromatic compound such as benzene in the presence of a Lewis acid. The product has the formula



where R_2 is H or halogen.

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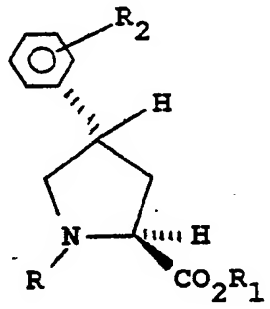
PROCESS FOR PREPARING (TRANS)-4-PHENYL-L-PROLINE DERIVATIVES

The present invention relates to a process for preparing trans-4-phenyl-L-proline derivatives which are intermediates in the preparation of certain angiotensin-converting enzyme inhibitors.

In accordance with the present invention, a process is provided for preparing (trans)-4-phenyl-L-proline derivatives of the structure I

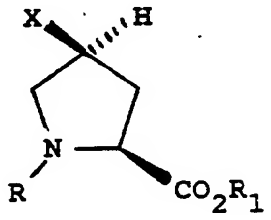


I

wherein R is a nitrogen protecting group (such as acetyl, benzoyl, p-anisoyl, p-nitrobenzoyl, trifluoroacetyl, o-toluoyl, p-toluoyl, p-tosyl, p-chlorobenzoyl, o-chlorobenzoyl, and the like,

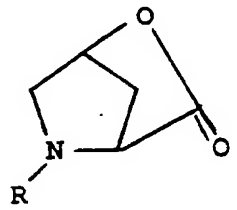
R_1 is H, aryl or lower alkyl, and R_2 is H, F, Cl or Br in the o or p positions or mixtures, which process includes the steps of reacting a proline derivative of the structure II

II



or a lactone of the structure III

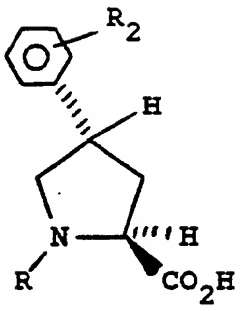
III



wherein R and R_1 are as defined above, and X is a leaving group (such as a halogen like F, Cl, Br or I, mesylate, tosylate or triflate), with an aromatic nucleophile such as benzene, halo-substituted benzene (e.g., F-, Cl- or Br-substituted benzene) or phenyltrimethyl silane, in the presence of a Lewis acid and, if desired, recovering the trans-4-phenyl-L-proline derivative from the reaction mixture. However, where the lactone III is employed, it is preferred that III be reacted with benzene.

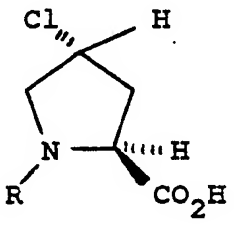
Where the lactone reactant III is employed, the trans-4-phenyl-L-proline derivative will have the structure

IV



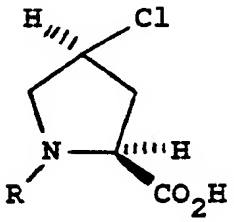
The reaction products resulting from using the lactone starting compound III will include the trans-4-phenyl-L-proline derivative I, as well as the side products

V



and

VI



Where the proline derivative II is employed as the starting compound, the reaction products obtained will include the trans-4-phenyl-L-proline derivative I as well as the side product V where the leaving group X in II is mesylate or F. In

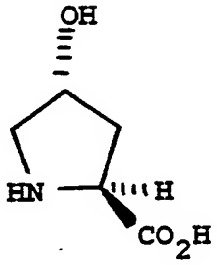
addition, where X in proline derivative II is Cl or tosylate, then cis-4-phenyl-L-proline may be obtained as a by-product as well.

The side product V may be converted to the neutral lactone III by treatment of the mixture of IV and V with a base such as sodium bicarbonate in the presence of an inert organic solvent such as dimethylformamide, at a temperature within the range of from about 0 to about 100°C and preferably from about 50 to about 80°C.

In carrying out the process of the invention, the proline derivative II or the lactone III will be employed in a molar ratio to the aromatic nucleophile of within the range of from about 1:5 to about 1:100 and preferably from about 1:10 to about 1:40, while the Lewis acid will be employed in a molar ratio to II or III of within the range of from about 2:1 to about 10:1 and preferably from about 3.6:1 to about 4.0:1. The reaction will be carried out at a reduced temperature of within the range of from about 5 to about 80°C and preferably from about 7 to about 40°C, under an inert atmosphere such as argon or nitrogen, depending upon the proline derivatives II or lactone III that is employed.

The starting lactone III may be prepared starting with the (trans)-4-hydroxy-L-proline

A

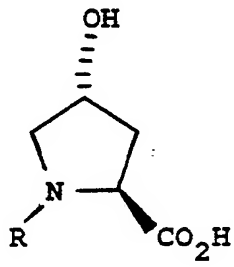


which is treated with a protecting compound

B RCl

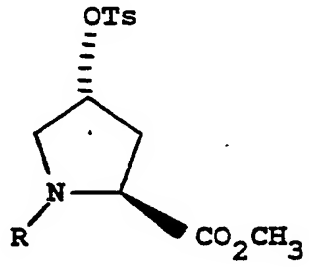
wherein "R" represents a nitrogen protecting group such as acetyl, benzoyl, p-anisoyl, p-nitrobenzoyl, trifluoroacetyl, o- or p-toluoyl, p-tosyl, or p- or o-chlorobenzoyl to form the protected proline derivative C

C



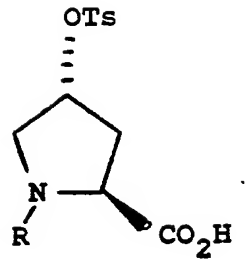
Proline C is then treated with p-TsOH (that is p-toluenesulfonic acid monohydrate) in the presence of methanol and then with p-TsCl and a base such as triethylamine or pyridine to form the tosylate D

D



which is treated with strong base such as sodium hydroxide to form the acid E

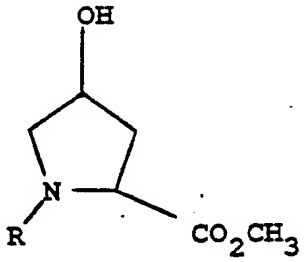
E



Acid E is then treated with weak base such as potassium carbonate in the presence of methylethyl ketone to form the lactone III.

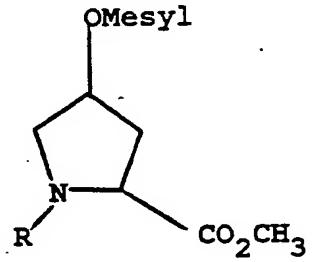
The starting derivative II when X is mesyloxy may be prepared by treating lactone III with methanol in the presence of an acid catalyst to afford hydroxy ester F

F



Treatment of F with methanesulfonyl chloride and a base such as triethylamine affords mesyl ester G

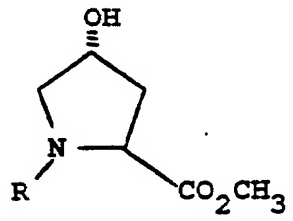
G



Treatment of G with lithium hydroxide affords II where X is mesyloxy.

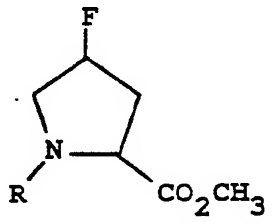
The starting proline derivative II wherein X is F may be prepared by treating a proline derivative of the structure

C'



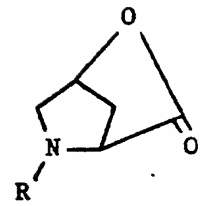
with diethylaminosulfur trifluoride and pyridine at a temperature within the range of from about -35°C to about 25°C employing a molar ratio of trifluoride:C' of within the range of from about 3:1 to about 1:1 in the presence of an inert organic solvent such as dichloromethane, to form the fluoro analog G

G

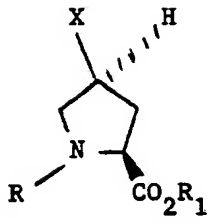


which is subjected to a saponification reaction by treatment with lithium hydroxide to form proline II where X is F.

Examples of starting lactone compounds III and starting proline compounds II useful in carrying out the process of the invention include, but are not limited to, the following.



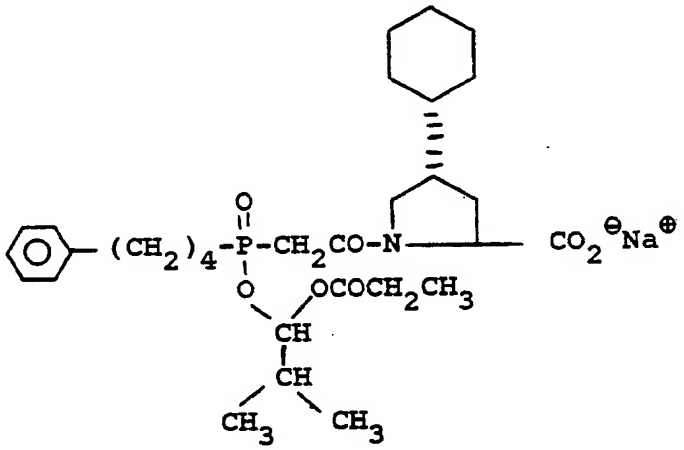
R
$C_6H_5C(=O)-$
$C_6H_5OC(=O)-$
$p\text{-}CH_3OC_6H_4C(=O)-$
CH_3SO_2-
$p\text{-}NO_2C_6H_4-$
$CH_3C(=O)-$
$CF_3C(=O)-$
$p\text{-}CH_3\text{-}C_6H_4C(=O)-$
$o\text{-}CH_3\text{-}C_6H_4C(=O)-$
p-tosyl-
$p\text{-}Cl\text{-}C_6H_4C(=O)-$
$o\text{-}Cl\text{-}C_6H_4C(=O)-$



X	R	R_1
F	$C_6H_5C(=O)-$	H and CH_3
Cl	$C_6H_5C(=O)-$	H
Cl	$C_6H_5OC(=O)-$	CH_3-
Br	$C_6H_5C(=O)-$	C_6H_5-
mesylate	$C_6H_5C(=O)-$	C_6H_5-
triflate	CH_3SO_2-	H and CH_3
triflate	$C_6H_5C(=O)-$	CH_3 and H
Cl	p-NO_2-C_6H_4-	C_6H_5-
Br	$CH_3C(=O)-$	H
I	CF_3-$C(=O)-$	H
mesylate	$C_6H_5C(=O)-$	H and CH_3
mesylate	o-Cl-$C_6H_4C(=O)-$	CH_3 and H

X	R	R_1
tosylate	$C_6H_5C(=O)$	H and CH_3
Cl	p-tosyl	$n\text{-}C_3H_7$
Br	o-Cl-$C_6H_4C(=O)$	$n\text{-}C_4H_9$
F	o-Cl-$C_6H_4C(=O)$	H and CH_3

The trans-4-substituted-4-phenyl-L-proline derivatives I may be employed to form angiotensin converting enzyme inhibitors as described in U. S. Patent No. 4,337,201 to Petrillo which covers fosinopril which has the following formula:



Listed below are definitions of the terms used in this specification. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances), either individually or as part of a larger group.

The terms "alkyl" and "alkoxy" refer to both straight and branched chain groups. Those groups having 1 to 10 carbon atoms are preferred.

The terms "cycloalkyl" and "cycloalkenyl" refer to groups having 3 to 7 carbon atoms.

The term "aryl" refers to phenyl or phenyl substituted with halogen, alkyl, alkoxy, alkylthio, hydroxy, alkanoyl, nitro, amino, dialkylamino, or trifluoromethyl groups.

The term "alkanoyl" refers to groups having 2 to 9 carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The following working Examples represent preferred embodiments of the present invention. Unless otherwise indicated, all temperatures are expressed in degrees Centigrade.

Example 1

(trans)-1-Benzoyl-4-phenyl-L-proline

A. 1-Benzoyl-allo-hydroxy-L-proline lactone

A(1) (trans)-1-Benzoyl-4-hydroxy-L-proline

A 12-liter beaker equipped with an efficient shaft stirrer, a pH electrode and a 1-liter dropping funnel was installed in an ice bath. 4 Liters of water were charged to the beaker, and 1.31 kg (10.0 moles) of trans-4-hydroxy-L-proline was added with agitation to dissolve same. The dropping funnel was then charged with aqueous 10N sodium hydroxide solution. The pH of the mixture was raised to 8.0 with a little sodium hydroxide solution (about 25 ml). 300 ml of benzoyl chloride was then added and the agitation speed raised to assure efficient dispersion. Sodium hydroxide solution was added as required to maintain pH 8 and sufficient cooling was provided to maintain the mixture at about 25°C. As soon as most of the benzoyl chloride was consumed, another 300 ml portion of benzoyl chloride was added and the benzoylation continued. Two more 300 ml portions of benzoyl chloride were added in sequence. The benzoylation was allowed to come to completion at pH 8 and the

mixture was stirred for an extra half hour while cooling to about 20°C.

A 4-liter separatory funnel was charged with 1 liter of isobutyl acetate. Part of the reaction mixture was added and equilibrated. The lower phase was allowed to settle and drain through a polish filter. More of the reaction mixture was added to the funnel until the total had been extracted. The IBA extract was discarded. The filtrate was returned to the 12-liter beaker and the dropping funnel was charged with concentrated hydrochloric acid. About 0.25 liters acid was added with efficient agitation to reach pH 4. Product seeds were added and agitation continued until a thin crystal slurry was formed and the pH did not climb anymore. Dropwise acid addition was resumed until the pH of the mixture was stable at 2.0. The total acid consumption was about 0.85 liters.

The crystal slurry was cooled to about 15°C and agitated for an additional half hour.

The sandy crystals were collected on a Buchner filter with most of the mother liquor being removed by suction. Then the crystals were washed with cold water until the filtrate was free of chloride ions. Suction was continued until no more liquid emerged. The product was then dried to constant weight.

A(2) (trans)-1-Benzoyl-4-hydroxy-L-proline, methyl ester

A 5-liter flask was installed in an oil bath on a magnetic stirrer, provided with a reflux

condenser and charged with 3.0 liters of methanol and 750 g (3.2 moles) of (trans)-1-benzoyl-4-hydroxy-L-proline. 19 grams of p-toluenesulfonic acid monohydrate (0.1 moles) were added. The mixture was heated to reflux and the esterification followed by TLC. Refluxing was continued until starting material was no longer detectable. 8 grams (0.1 moles) of sodium acetate was added to neutralize the catalyst acid. The condenser was set for distillation and the mixture concentrated at atmospheric pressure until the pot temperature reached 80°C. The distillate was then discarded. The clear residue was rapidly diluted with 2 liters of warm water. The flask was swirled for quick mixing and to permit the ester to crystallize. The slurry was cooled to room temperature with occasional swirling and maintained at room temperature for at least another hour. The crystals were collected on a filter and the filtrate recycled to aid in the transfer. The cake was pressed down and washed with one liter of cold water. The cake was sucked dry as possible and the product dried via a laboratory fluid bed dryer to constant weight. The combined filtrate was vacuum concentrated from the first crop to a small volume and the resulting slurry cooled to room temperature. A second crop of crystals was collected on a filter and washed with a minimum of cold water. The cake was pressed down and suction applied until no more liquid emerged. The second crop was dried to constant weight.

A(3) (trans)-1-Benzoyl-4-tosyloxy-L-proline methyl ester

540 Grams (2.84 moles) of technical p-toluenesulfonyl chloride were charged to a 5 liter flask. 1.5 Liters of anhydrous pyridine was added and the flask swirled to dissolve. Gradually, 600 g (2.40 moles) of (trans)-1-benzoyl-4-hydroxy-L-proline methyl ester were added and dissolved by swirling. The clear solution was maintained at room temperature and the conversion followed by TLC. After the starting material completely disappeared, the reaction mixture was transferred to a 12 liter beaker with an efficient agitator. 0.8 Liters of ice water and some tosylate seeds were added. Thick crystal slurry formed in about 10 minutes. Strong agitation was maintained and another 7 liters of an ice-water mixture were added over a period of one hour. The crystals were collected on a filter, the cake pressed down and washed with cold water until the effluent was free of chloride ions and suction applied to the cake until no more liquid emerged. The filtrate was discarded and the product dried to constant weight.

A(4) (trans)-1-Benzoyl-4-hydroxy-proline-tosylate

To a mixture of 6 liters of aqueous NaOH (81.6 g, 4.15 moles NaOH) and 1.6 liters of methanol were added Part A(3) tosylate (806.9 g, 2 moles) while holding the temperature between 25-30°C. The mixture was stirred for 24 hours while holding the pH of the mixture between

11.0-11.5. The reaction mixture was filtered clear, the pH adjusted to 2.0 by addition of 37% aqueous hydrochloric acid (ca 175 ml) and stirring was continued for 1 hour at 20°C. The product was collected by filtration and the cake washed with water until Cl^- test was nearly negative. Wet weight: 2400 g. The product was dried at 40°C to a water content less than 5% by K.F.

Yield: 762.6 g = 97.9 % "as is"
= 93.4 % corrected for H_2O

A(5) 1-Benzoyl-allo-hydroxy-L-proline-lactone

15 Liters of methyl ethyl ketone were added to a 50 liter reactor, followed by 731.6 g Part A(4) tosylate. 573.2 g K_2CO_3 were added with good agitation. The mixture was heated to reflux and held at reflux until TLC in-process control showed that reaction was complete. The reaction mixture was cooled to 15-20°C and the undissolved K_2CO_3 collected by filtration and washed with 15 liters of methyl ethyl ketone. The product rich filtrate was concentrated to about 1200-1300 g under reduced pressure. 2.3 Liters of n-hexane were added within 1 hour and the mixture stirred for 1 hour at 20°C. The precipitated title lactone was collected by filtration and washed with 700 ml of n-hexane. Wet weight: 532 g. The material was dried in vacuo to a constant weight of 332.7 g, 79.4%.

B. (cis)-1-Benzoyl-4-hydroxy-L-proline, methyl ester

A suspension of Part A lactone (100 g, 460.8 mmoles) in 2 liters of methanol was treated with p-toluenesulfonic acid monohydrate (1.28 g). The reaction was stirred 2 days at room temperature under argon. The methanol was removed in vacuo from the resulting solution. The residue was taken up in 1.4 liters of EtOAc, washed with saturated $NaHCO_3$ solution (3 x 300 ml), water (100 ml), and brine (100 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid was recrystallized from EtOAc (100 ml), filtered, washed with cold EtOAc and dried in vacuo to yield 81.25 g (71%) of title compound.

M.P. 102.5-104°C

Anal Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62

Found: C, 62.87; H, 6.03; N, 5.57

C. (cis)-1-Benzoyl-4-[(4-methylsulfonyl)-oxy]-L-proline

A solution of Part B proline derivative (80 g, 321.3 mmoles) in 1.6 liters of dichloromethane was treated with Et_3N (67.17 ml, 482 mmoles). The solution was cooled to -15°C in an acetone-dry ice bath and methanesulfonyl chloride (28.3 ml, 353 mmoles) was added via addition funnel. The reaction was very exothermic and care had to be taken to keep the temperature below -5°. After stirring for 30 minutes at -5°C to -10°C, TLC (9:1

CH_2Cl_2:HOAc) indicated the reaction had gone to completion. The dichloromethane was removed in vacuo. The residue was taken up in ethyl acetate (1.5 liters), washed with 2 x 400 ml of water, 2 x 400 ml of 1 N HCl, 400 ml of saturated $NaHCO_3$ solution, 400 ml of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to a viscous oil. The oil was treated with 1 liter of THF (from a fresh bottle) and 200 ml of water. $LiOH \cdot H_2O$ (28.31 g, 674.7 mmoles) was added and the reaction was stirred for one hour. The THF was removed in vacuo and the pH was lowered to 1 with concentrated HCl. The aqueous mixture was extracted with 2 x 400 ml of ethyl acetate and the extracts were washed with 250 ml of water and then brine. At this point the extracts started to crystallize so they were transferred to an Erlenmeyer flask and recrystallized after boiling off 250 ml of ethyl acetate. The crystals were collected by filtration, washed with cold ethyl acetate and hexane, and dried in vacuo to yield 69.18 g of title compound as white prisms (69%).

M.P. 172-173°C (with decomposition)

Anal Calcd for $C_{13}H_{15}NO_6S \cdot 0.05\ H_2O$:
C, 49.69; H, 4.84; N, 4.46

Found: C, 49.48; H, 4.79; N, 4.42

D. (trans)-1-Benzoyl-4-phenyl-L-proline

A dry, 3-necked 2l Morton flask (equipped with overhead stirrer, nitrogen inlet, and temperature probe) was charged with anhydrous aluminum chloride (124.23 g, 0.93 mole) followed

by thiophene free benzene (810 ml). While stirring, the flask was cooled (dry ice-acetone) to an internal temperature of 6°C. Part C compound (powdered) was added (81 g, 0.26 mole) in portions. A rise in internal temperature to 7°C was noted after the addition of ca. half the solid. The addition was briefly interrupted until the internal temperature returned to 6°C and was then continued. The resulting heterogeneous mixture was vigorously stirred for 4 hours at 7-8°C and 1.5 hours at 8-10°C. During this time the reaction became almost totally homogeneous and TLC indicated the conversion of Part C compound to a mixture of the title compound and (trans)-1-benzoyl-4-chloro-L-proline. The reaction was cooled to 7°C, and the mixture was hydrolyzed by the slow addition of 3N HCl (990 ml) such that the internal temperature did not rise above 30°C. The hydrolyzed mixture was treated with brine (180 ml), seeded with crystals of title compound, stirred at room temperature for 45 minutes and then held at room temperature overnight. The mixture was filtered through a coarse frit and the solid remaining in the reaction vessel was transferred to the funnel using 1N HCl (390 ml). The crude product was washed with water (4 x 500 ml). The last filtrate gave a weakly positive test for chloride (ethanolic silver nitrate). After drying on the filter for ca. 20 minutes the product weighed 122 g (159 mole%). The product was dried <u>in vacuo</u> to a weight of 98 g. The crude product was suspended in 240 ml of n-butyl acetate and heated to boiling. When the product dissolved, a second lower layer (presumably

residual water) was evident. Boiling was continued until this layer disappeared. Sodium sulfate was added, boiling was continued an additional 5 minutes, and the mixture was filtered through celite (pre-washed with n-butyl acetate). The celite was washed with hot n-butyl acetate (2 x ca. 50 ml). The filtrate volume was reduced to 240 ml, cooled, was seeded with crystals of title compound and stirred gently at ambient temperature overnight. The crystals were filtered and washed with n-butyl acetate (1 x 50 ml) and hexane (1 x 50 ml). The product was dried under high vacuum at 40°C to a constant weight of 57.37 g (75.1 mole %; corrected for starting material and product HI). HPLC HI (λ218) of 99.03.

M.P. 137-138.5°C

$[\alpha]_D$ = -62.3° (c=1.0, MeOH)

Anal Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74

Found: C, 73.10; H, 5.81;, N, 4.72

Examle 1A

(trans)-1-Benzoyl-4-phenyl-L-proline

A suspension of aluminum trichloride (7.456 g, 55.91 mmole) in benzene (150 ml) was stirred under argon and treated with powdered (cis)-1-benzoyl-4-mesyloxy-L-proline (5 g, 15.93 mmole). The reaction was stirred at room temperature for 7 hours, cooled and treated slowly with 1N HCl (55 ml). After stirring 15 minutes, the mixture was transferred to a separatory funnel and treated with an additional 55 ml of 1N HCl

followed by 20 ml of concentrated HCl and 250 ml of ethyl acetate. The layers were separated and the aqueous layer was washed with additional ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water and brine and dried. Filtration and concentration in vacuo afforded 4.74 g of a white foam which was recrystallized from n-butyl acetate (seeding and sonication to initiate crystallization). The product was filtered, washed with n-butyl acetate and hexane, and dried in vacuo to 2.168 g of (trans)-1-benzoyl-4-phenyl-L-proline.

The mother liquor was evaporated and treated with DMF (50 ml) and potassium bicarbonate (868 mg). The resulting solution was stirred at 60-65°C under argon for 5 hours, treated with additional potassium bicarbonate (100 mg) and stirred an additional 2 hours. THe DMF was mostly removed in vacuo at 35°C and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer (A) was washed twice with potassium bicarbonate solution. The combined aqueous extracts were acidified to pH 1.5 with HCl, extracted with ethyl acetate and washed with 1N HCl, water, brine and dried. Filtration and concentration in vacuo afforded 1.683 g (corrected for residual solvent) of (trans)-1-benzoyl-4-phenyl-L-proline. The overall yield for the experiment was (2.168 g + 1.683 gm) 81%.

The ethyl acetate layer (A) from above was washed with brine, dried, filtered and concentrated in vacuo to 312 mg of 1-benzoyl-allo-hydroxy-L-proline lactone.

Example 2

(trans)-1-Benzoyl-4-phenyl-L-proline

A suspension of aluminum trichloride (736 mg, 4.8 mmole) in benzene (5 ml) was treated with N-benzoyl-allo-hydroxy-L-proline lactone (prepared as described in Example 1, Part A) (217 mg, 1 mmole) and stirred under argon at 45°C for 2 hours. After removal of the heat, the reaction was allowed to stand at room temperature overnight. Hydrolysis was effected by pouring the mixture into cold, aqueous HCl followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with 4% acetic acid-dichloromethane to afford:

(a) (trans)-1-Benzoyl-4-phenyl-L-proline (119 mg, 40%)

(b) (trans)-1-Benzoyl-4-chloro-L-proline (70 mg, 28%)

(c) (cis)-1-Benzoyl-4-chloro-L-proline: present by TLC in several mixed fraction 1 with (b).

Example 3

(trans)-1-Benzoyl-4-phenyl-L-proline

A. (cis)-1-Benzoyl-4-fluoro-L-proline methyl ester

A solution of (trans)-1-benzoyl-4-hydroxy-L-proline methyl ester prepared as described in Example 1 Part A(2) (6 g, 24.1 mmole) was dissolved in dichloromethane and cooled to -45°C under an argon atmosphere. To the above solution diethylaminosulfur trifluoride (5.2 ml, 42 mmole)

was added dropwise. The resulting solution was stirred and warmed to -35°C. To the above solution pyridine was added dropwise (9 ml, 116 mmole). The reaction was allowed to stir overnight while warming to room temperature. The solvent was removed in vacuo and the oily residue treated with ethyl acetate and 1N HCl. The mixture was transferred to a separatory funnel, the aqueous layer removed, and the organic layer washed with additional 1N HCl, then water and saturated sodium bicarbonate solution. The organic solution was dried over sodium sulfate, filtered and concentrated to a yellow oil. The crude product was chromatographed on silica gel using 1:1 ethyl acetate:hexane as eluent. Combination and concentration of product containing fractions produced 3.9 gm (64%) of title compound as an oil.

B. (cis)-1-Benzoyl-4-fluoro-L-proline

To a solution of Part A (cis)-1-benzoyl-4-fluoro-L-proline methyl ester (3.7 g, 14.74 mmole) in tetrahydrofuran-water (37 ml-7 ml) was added 31 ml of a 1N solution of lithium hydroxide in water. The reaction was stirred at room temperature for 2 hours. The tetrahydrofuran was evaporated, the pH of the residual aqueous solution was adjusted to 8 and extracted with ethyl acetate. The organic extracts were discarded. The aqueous phase was acidified to pH 2 with concentrated HCl and extracted with dichloromethane. The organic extracts were washed with brine and dried (sodium sulfate). The

organic solution was filtered and concentrated to 2.9 g of solid.

The crude product was recrystallized by dissolving in ca. 100 ml of boiling ethyl acetate. The volume was reduced to ca. 75 ml, cooled and crystallization was allowed to proceed at room temperature overnight. The product was filtered, washed with ethyl acetate and hexane and dried <u>in vacuo</u> to 2.32 g (66%). M.P. 195-197°C.

Anal Calcd for $C_{12}H_{12}NO_3F$: C, 60.76; H, 5.10; N, 5.91; F, 8.01

Found: C, 60.62; H, 5.09; N, 5.88; F. 8.23

C. <u>(trans)-1-Benzoyl-4-phenyl-L-proline</u>

A suspension of aluminum trichloride (191 mg, 1.43 mmole) in benzene (5 ml) was stirred under argon and treated with Part B (cis)-N-benzoyl-4-fluoro-L-proline (100 mg, 0.42 mmole). The reaction was stirred at room temperature for 20 hours, cooled to 0°C and hydrolyzed with 1N HCl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried and concentrated. The residue consisted of (a) (trans)-1-benzoyl-4-phenyl-L-proline (70%) (b) (trans)-1-benzoyl-4-chloro-L-proline (30%). The ratios were determined by spectrodensitometry at λ 260.

Example 4

(trans)-1-o-Chlorobenzoyl-4-phenyl-L-proline

A. (cis)-1-o-Chlorobenzoyl-4-fluoro-L-proline

A solution of (cis)-4-fluoro-L-proline hydrobromide (Biochemistry, 4(11), 2507 (1965); 250 mg, 1.17 mmole) in 4 ml of water was prepared. The pH was adjusted to 7.8 with aqueous potassium carbonate. o-Chlorobenzoyl chloride (155 µl, 1.23 mmole) was added in three portions while maintaining the pH at 7.5-8.0. After the pH was stabilized, the reaction was transferred to a separatory funnel and washed with several portions of ethyl acetate. The aqueous layer was acidified to pH 2 with concentrated HCl, saturated with sodium chloride and extracted with ethyl acetate. The organic extracts were washed with brine, dried (sodium sulfate), filtered and concentrated to a solid. The crude product was recrystallized from ethyl acetate, filtered, washed with cold ethyl acetate and hexane and dried in vacuo to 204 mg (64%). M.P. 158-160°C.

Anal Calcd for $C_{12}H_{11}ClFNO_3$: C, 53.05; H, 5.16; N, 5.16; Cl, 13.05, F, 6.99

Found: C, 53.25; H, 4.12; N, 5.17;, Cl, 12.86; F, 7.35

B. (trans)-1-o-Chlorobenzoyl-4-phenyl-L-proline

A suspension of aluminum trichloride (100 mg, 0.75 mmole) in benzene (3.7 ml) was stirred under argon and treated with (cis)-1-o-chlorobenzoyl-4-fluoro-L-proline (60 mg, 0.22 mmole).

After stirring overnight, the reaction was cooled, quenched with 1N HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated in vacuo. The residue consisted of

	Yields	
	λ260	NMR
(a) trans-1-o-chlorobenzoyl-4-phenyl-L-proline	83%	85%
(b) trans-1-o-chlorobenzoyl-4-chloro-L-proline	17%	15%

Mass spectroscopy confirmed the presence of both products.

The stereochemistry of the products in this example was assumed to be trans based on the result for Example 3.

Example 5

(trans)-1-Benzoyl-4-phenyl-L-proline

A. (cis)-1-Benzoyl-4-chloro-L-proline

(trans)-N-benzoyl-4-hydroxy-L-proline methyl ester (prepared as described in Example 1 Part A(2) (4.0 g, 16.19 mmoles) was added neat in several portions to a stirred solution of benzene (25 ml), carbon tetrachloride (2.19 ml, 22.67 mmoles) and triphenylphosphine (5.95 g, 22.67 mmoles) at room temperature. Acetonitrile (15 ml) was added and the reaction was stirred for 16 hours. The solvents were removed in vacuo and the residue was treated with THF (50 ml) and 32.4 ml of 1N sodium hydroxide solution. The reaction was stirred at room temperature for 4 hours. The organic solvent was removed in vacuo and the

aqueous solution was extracted with ethyl acetate. The cooled aqueous solution was acidified to pH 2 with concentrated hydrochloric acid, then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated in vacuo to a white solid. This solid was recrystallized from ethyl acetate to yield 2.5 g (61%) of (cis)-1-benzoyl-4-chloro-L-proline.

M.P. 167.5°C.

Anal Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.81; H, 4.77; N, 5.52; Cl, 13.97

Found: C, 56.97; H, 4.82; N, 5.57; Cl, 13.70

B. (trans)-1-Benzoyl-4-phenyl-L-proline

A suspension of aluminum trichloride (452 mg, 3.4 mmole) in benzene (5 ml) was stirred under argon and treated with (cis)-1-benzoyl-4-chloro-L-proline (253 mg, 1 mmole). The reaction was stirred at reflux overnight, cooled and hydrolyzed with 1N HCl. The mixture was extracted with ethyl acetate. The organic extracts were washed with water, dried and concentrated in vacuo. Filtration and concentration in vacuo afforded a mixture consisting of:

(a) (trans)-1-benzoyl-4-phenyl-L-proline (75%)
(b) (cis)-1-benzoyl-4-phenyl-L-proline (16.5%)
(c) (cis)-1-benzoyl-4-chloro-L-proline (2%)
(d) (trans)-1-benzoyl-4-chloro-L-proline (6.4%)

The yields were determined by spectrodensitometry at λ260.

Example 6

(trans)-1-Benzoyl-4-phenyl-L-proline

A. (cis)-1-Benzoyl-4-tosyloxy-L-proline, methyl ester

A solution of (cis)-1-benzoyl-4-hydroxy-L-proline, methyl ester (1.9 g, 7.63 mmole) in pyridine (6 ml) was stirred under argon and treated with p-toluenesulfonyl chloride (1.75 g, 9.16 mmole). The reaction was stirred overnight, treated with additional p-toluenesulfonyl chloride (0.145 g, 0.76 mmole) and stirred for 24 hours. Ice water was added followed by ethyl acetate. The organic layer was washed with 1N HCl, brine, and dried. Filtration and concentration in vacuo afforded the title compound as a foam which was used without purification in the subsequent step.

B. (cis)-1-Benzoyl-4-tosyloxy-L-proline

A solution of (cis)-1-benzoyl-4-tosyloxy-L-proline, methyl ester (from the previous step) in THF·H_2O (25 ml - 5 ml) was stirred under argon and treated with lithium hydroxide mono hydrate (672 mg, 16 mmole). The reaction was stirred for 3 hours, concentrated in vacuo, acidified to pH 1.5 with HCl, and extracted with ethyl acetate. The organic extracts were dried, filtered and concentrated in vacuo to a white solid which was recrystallized twice from ethyl acetate to afford the title compound.

C. (trans)-1-Benzoyl-4-phenyl-L-proline

To a dry flask was added aluminum trichloride (58 mg, 0.435 mmole) and benzene (3

ml). While stirring under argon, (cis)-1-benzoyl-4-tosyloxy-L-proline (50 mg, 0.128 mmole) was added. After further stirring overnight, the reaction was cooled to 0°C and quenched with 1N HCl. The resulting mixture was extracted with ethyl acetate and the organic extracts were washed with brine, dried, and concentrated in vacuo. The residue consisted of:

		% (densitometry, λ260)
(a)	(trans)-1-Benzoyl-4-phenyl-L-proline	66%
(b)	(trans)-1-Benzoyl-4-chloro-L-proline	17%
(c)	(cis)-1-Benzoyl-4-phenyl-L-proline or	17%
(d)	(cis)-1-Benzoyl-4-tosyloxy-L-proline	

or a mixture of (c) and (d) which was not separable by tlc.

Example 7

(trans)-1-Benzoyl-4-phenyl-L-proline

A suspension of powdered (cis)-1-benzoyl-4-mesyloxy-L-proline (250 mg, 0.8 mmole) in 1,2-dichlorobenzene (3 ml) was stirred under argon and treated with phenyltrimethylsilane (1 ml, 5.8 mmole) followed by aluminum trichloride (383 mg, 2.87 mmole). The reaction was stirred overnight and an aliquot was removed, quenched into 1N HCl and extracted with ethyl acetate. Analysis of the organic layer by tlc showed the presence of :

(a)	(trans)-1-benzoyl-4-phenyl-L-proline	41%
(b)	(trans)-1-benzoyl-4-chloro-L-proline	59%

Yield by densitometry at λ260.

Example 8

(cis)-1-Benzoyl-4-chlorophenyl-L-proline

A suspension of aluminum trichloride (364 mg, 2.72 mmole) in chlorobenzene (10 ml) was stirred at 0°C under argon and treated with powdered (cis)-1-benzoyl-4-mesyloxy-L-proline. The reaction was stirred at 0°C for 3 hours and room temperature overnight. The reaction was quenched at 0°C by the addition of 1N HCl. The mixture was diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution. The aqueous layer was acidified to pH 2 with HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried, filtered and concentrated in vacuo. Mass spectral analysis indicated the presence of

(a) (trans)-1-benzoyl-4-chlorophenyl-L-proline and

(b) (trans)-1-benzoyl-4-chloro-L-proline.

Spectrodensitometry of a HC plate showed the ratio of a:b was 32:68 (λ260).

Example 9

Alternative Preparation of (cis)-1-Benzoyl-4-mesyloxy-L-proline

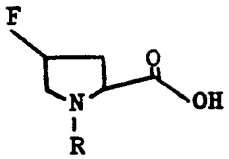
A solution of (cis)-1-benzoyl-4-hydroxy-L-proline, methyl ester (169.2 g, 0.679 mole) and triethylamine (104.2 ml, 0.747 mole) in dichloromethane (3.3 liters) was cooled to -10°C under nitrogen and treated dropwise with methanesulfonyl chloride (59.85 ml, 0.74 mole). The reaction was stirred an additional 30 minutes at -5°C to -10°C and the volatiles were removed in vacuo. The

residue was treated with ethyl acetate and washed with water, 1N HCl, saturated sodium bicarbonate solution, and brine. The organic solution was dried, filtered, and concentrated in vacuo. The residue was dissolved in THF (2.1 liters) and treated with 3.36 N LiOH solution (423 ml) and stirred at room temperature for 1 hour. The THF was removed in vacuo and the aqueous solution was acidified to pH 4. The resulting solid was filtered, washed with ice water, and recrystallized from 95% ethanol-ethyl acetate to afford 130 g of the title compound.

Example 10 to 20

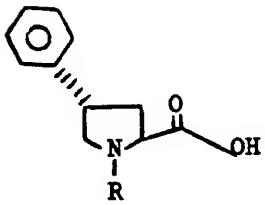
Following the procedure of Example 3 except substituting the (cis)-1-R-4-fluoro-L-proline shown in Column I below for the (cis)-1-benzoyl-4-fluoro-L-proline used in Example 3, the following products IIx and IIx were obtained.

Column I



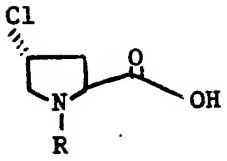
Ix

Column II*



IIx

Column III*



IIIx

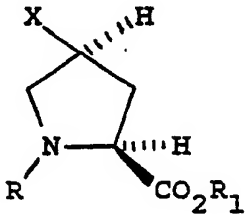
Ex. No.	R	TLC (λ260) IIx	TLC (λ260) IIIx	% of IIx (PMR)
10.	p-anisoyl	34	32	and 2 demethylated products (15%, 19%). Required 4.4 equiv $AlCl_3$
11.	p-nitrobenzoyl	40	46	and 13.6% Ix. Used 5 equiv $AlCl_3$
12.	phenoxycarbonyl	50	50	
13.	acetyl			53
14.	trifluoroacetyl			63
15.	o-toluoyl	64	36	
16.	p-toluoyl	65	35	62
17.	p-tosyl	66	34	69
18.	benzoyl	70	30	
19.	p-chlorobenzoyl	74	26	73
20.	o-chlorobenzoyl	83	17	84

*Trans stereochemistry confirmed for entry 14 by comparison with authentic samples.

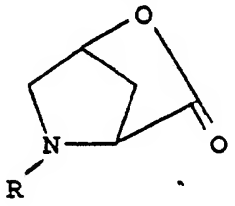
For examples 12-13 and 16-20, mass spectroscopy confirmed the presence of IIX and IIIX.

CLAIMS

1. A process for preparing (trans)-4-phenyl-L-proline derivatives, which comprises reacting a proline derivative of the structure

(II) 

or a proline lactone of the structure

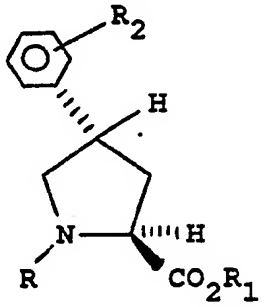
(III) 

wherein R is a nitrogen protecting group;

R_1 is H, aryl or lower alkyl; and

X is a leaving group,

with an aromatic nucleophile in the presence of a Lewis acid as a catalyst, to form a reaction product containing the (trans)-4-phenyl-L-proline derivative of the structure

(I) 

wherein R and R_1 are as defined above, and R_2 is H or halo, provided that where the lactone starting material is employed, R_1 is H.

2. The process as defined in Claim 1 including the step of recovering the (trans)-4-phenyl-L-proline derivative from the reaction mixture.

3. The process as defined in Claim 1 or 2 wherein the aromatic nucleophile is benzene, halosubstituted benzene or phenyltrimethylsilane.

4. The process as defined in Claim 1 or 2 wherein the aromatic nucleophile is benzene or phenyltrimethylsilane

5. The process as defined in any preceding claim wherein the proline derivative used as a reactant is employed in a molar ratio to the aromatic nucleophile of within the range of from about 1.5:1 to about 1:100.

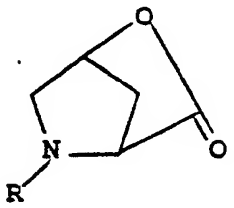
6. The process as defined in any preceding claim wherein the Lewis acid is aluminum chloride.

7. The process as defined in any preceding claim wherein the nitrogen protecting group is benzoyl, mesyl, p-anisoyl, p-nitrobenzoyl, acetyl, trifluoroacetyl, o-toluoyl, p-toluoyl, p-tosyl, p-chlorobenzoyl or o-chlorobenzoyl.

8. The process as defined in any preceding claim wherein the Lewis acid is employed in a molar ratio to the proline derivative or lactone reactant of within the range of from 2:1 to about 10:1.

9. The process as defined in any preceding claim wherein the X leaving group is halogen, mesylate, tosylate or triflate.

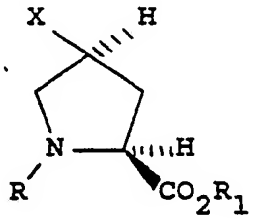
10. The process as defined in any preceding claim wherein the proline lactone



is reacted with benzene.

11. The process as defined in Claim 10 wherein R is benzoyl.

12. The process as defined in any one of Claims 1-9 wherein the proline derivative

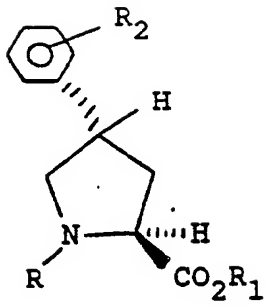


is reacted with benzene.

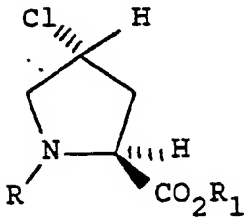
13. The process as defined in Claim 12 wherein R is benzoyl or 2-chlorobenzoyl.

14. The process as defined in Claim 12 or 13 wherein X is F or CH_3SO_2O- and R_1 is H.

15. The process as defined in Claim 1 wherein the reaction products include

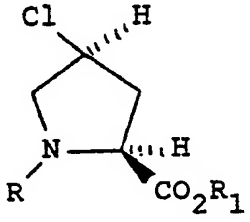


and

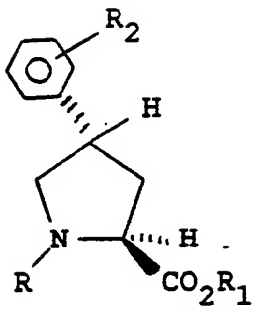


, and

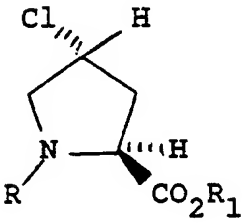
where the proline lactone is employed as the starting material, the reaction products also include



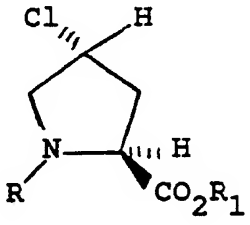
16. The process as defined in Claim 12 wherein X = F or mesyloxy, the reaction products include



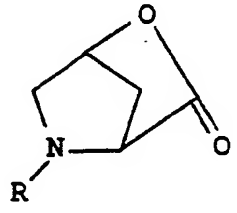
and



17. The process as defined in Claim 10 further including the step of treating the reaction product with a base to convert

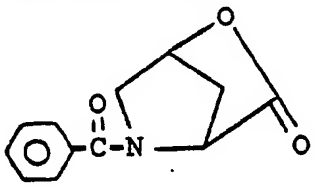


to the proline lactone



and extracting the lactone from the reaction mixture.

18. The process as defined in any one of Claims 1-9 wherein the proline derivative or proline lactone employed as a reactant has the structure



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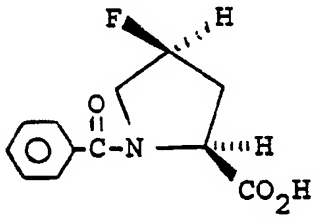

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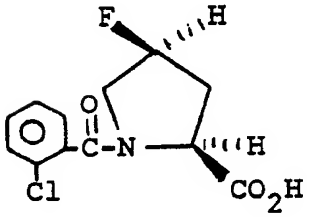
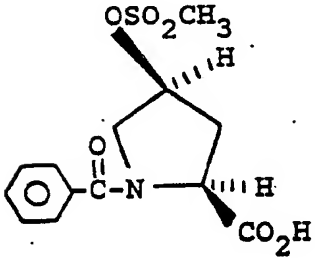


or



and the Lewis acid is $AlCl_3$.

19. The process as defined in any preceding claim wherein the reaction is carried out at a temperature within the range of from about 5 to about 80°C.

20. The process as defined in any preceding claim wherein the reaction is carried out in the presence of an inert organic solvent under an inert atmosphere.

21. A (trans)-4-phenyl-L-proline derivative of formula I as defined in Claim 1, when prepared by a process as defined in any preceding claim.

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